# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-335/S-003

# Medical Review(s)

CLINICAL REVIEW

# Supplemental NDA 21-335/S-003
# New Drug Application

## GLEEVEC ™ (imatanib mesylate)

FDA Center for Drug Evaluation and Research
Division of Oncology Drug Products

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Applicant: Novartis Pharmaceuticals Corporation

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# Clinical Review for sNDA 21-335/S-003

## *Executive Summary*

This multidisciplinary medical-statistical review addresses a supplement to NDA 21-335/S-003 for use of Gleevec for the treatment of pediatric patients with Ph+ chronic phase CML who have recurred after stem cell transplant or are resistant to interferon alpha therapy.

The current supplement presents the results of two Phase 1, open-label, multicenter, dose-finding studies (Study 0103 and Study 03001) of Gleevec administered to this patient population. Efficacy was a secondary objective for both studies. The sponsor is seeking an accelerated approval on the basis of a surrogate endpoint (response rate).

Gleevec is approved in the US for the following indications:
(1) Gleevec is indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML), in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. (2) Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal tumors (GIST).

## I. Recommendations

### A. Recommendation on Approvability

The Division of Oncology Drug Products recommends Gleevec as approvable under subpart H (Accelerated Approval) for children with Ph+ CML in chronic phase in recurrence after stem cell transplantation or after failure of interferon alpha therapy. FDA requirements for the approval of Gleevec in this patient population include: (1) Submission and approval of a chemistry supplement for a scored 100 mg tablet; (2) Labeling revisions. See FDA Review Team labeling revisions.

Support for the efficacy of Gleevec in children with Ph+ CML chronic phase is mainly extrapolated from adults with Ph+ CML. Two phase 1 studies (Study 0103 and Study 03001) are designed as dose-finding studies to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for anti-leukemic effects of Gleevec in pediatric patients with Ph+ leukemias. Cytogenic responses in 13 of 16 patients with evalable data confirm the efficacy in children. There are no controlled clinical trials demonstrating clinical benefit, such as improvement in disease related symptoms or improved survival.

The safety profile of Gleevec in children is consistent with the known toxicities observed in adult patients with the exception that peripheral edema and muscoloskeletal pain were less frequent in

children. Common toxicities included nausea, vomiting, diarrhea, and hematologic laboratory changes (neutropenia, thrombocytopenia, and anemia).

### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Applicant's Phase 4 commitment will be a satisfactory time-line for completion and submission of a study in children with Ph+ CML following the protocol for the Children's Oncology Group Phase 2 study previously submitted. This is conditional on changing the Gleevec dose in the protocol from 340 to 260 mg/m2.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

Imatinib (Gleevec, Novartis, Basel, Switzerland), formerly referred to as STI571 and CGP 57148B, is an inhibitor of specific protein tyrosine kinases that were targeted to the platelet-derived growth factor (PDGF) receptor. It was developed in a search for a selective kinase inhibitor of the active fusion product abl kinase.

Gleevec received accelerated approval under Subpart H of CRF 314.500 on May 10, 2001 on the basis of the response rates in patients with of Ph+ CML in three clinical settings: CML blast crisis, accelerated phase and chronic phase in adult patients after failure of interferon-alpha therapy.

Gleevec has also been approved for the treatment of patients with with kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Study 0103 and Study 03001, the subject of this review, were submitted to the FDA in August 2002.

### B. Efficacy

Study 0103 and Study 03001 were open-label, multicenter, dose-finding Phase 1 studies that were conducted on 39 pediatric patients with CML in chronic phase recurrent after stem cell transplant or resistant to interferon alpha therapy, or pediatric patients with Ph+ acute AML or ALL or CML in blast crisis refractory to or recurrent after a multi-drug therapy regimen.

Efficacy was a secondary endpoint in both studies. One study (0103) enrolled 31 pediatric patients with either Ph+ chronic phase CML (n=15) or in CML in blast crisis or Ph+ acute leukemias (n=16). Patients were treated at doses of 260 mg/m2/day (n=6), 340 mg/m2/day (n=11), 440 mg/m2/day (n=8) and 570 mg/m2/day (n=6). In 13 patients with chronic phase CML for whom cytogenetic data are available, 11 achieved a major cytogenetic response and 7

achieved a complete cytogenetic response. At the recommended dose of 260 mg/m2/day, 2 of 3 patients achieved a complete cytogenetic response.

In a second study 8 patients were treated with Gleevec doses ranging from 173 to 362 mg/m2. Three of these patients had Ph+ CML chronic phase, 4 patients had Ph+ acute leukemias, and 1 patient had lymphoid blast crisis. Two of the three CML patients achieved a complete cytogenetic response at doses of 242 and 257 mg/m2.

Overall the rate of complete cytogenetic response at the sponsor's recommended dose in children with Ph+ CML chronic phase recurrent after stem cell transplant or resistant to interferon-alpha therapy was 67% (4 of 6 patients).

### C. Safety

The safety profile of Gleevec given as an oral drug is contained in the current label based on clinical data in adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after interferon-alpha therapy and in patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal tumors (GIST).

The safety data in pediatric patients with Ph+ chronic phase CML who have recurred after stem cell transplant or are resistant to interferon-alpha therapy, are similar to the toxicities described in adult patients at the sponsor's recommended dose. Nausea, vomiting were the most common non-hematologic toxicities and occurred in approximately 83% of patients. Diarrhea was reported in 33% of children.

Grade 3 or 4 hematologic toxicities included neutropenia and thrombocytopenia in 50% of patients and anemia in 33% of patients. There were no treatment-related deaths on Study 0103. One patient with Ph+ ALL died during the Cycle 2 of treatment due to febrile neutropenia, Aspergillus pneumonia (Study 03001).

### D. Dosing

The recommended dose of Gleevec for pediatric patients with Ph+ CML chronic phase is 260 mg/m2/day administered orally as a once daily dose or alternatively the daily dose may be split into two – once in the morning and once in the evening.

### E. Special Populations

Both studies (Study 0103 and Study 03001) were conducted solely in children and adolescents with Ph+ CML chronic phase or in blast crisis or children with Ph+ acute leukemias who have recurred after stem cell transplant or are resistant to interferon-alpha therapy or multidrug chemotherapy regimens. Patients range in age from 3 to 20 years old. Among the CML patients

in Study 0103 three were 3-11 years old and 9 were between 12-18 years old. One patient was 19 and one patient was 20 years old.

## *Clinical Review*

## I. Introduction and Background

Chronic myeloid leukemia (CML) is a hematologic neoplasm associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome. The Ph chromosome is detected in 95% of patients with CML and in 20% of adults with acute lymphocytic leukemia (ALL). The molecular consequence of the translocation is the fusion of the Abl proto-oncogene to the BCR gene resulting in the production of an activated form of the Abl protein-tyrosine kinase. The Bcr-Abl protein is capable of inducing leukemia in mice, implicating the protein as the cause of these diseases. The tyrosine kinase activity of the Bcr-Abl protein is essential to its transforming ability.

CML progresses through three clinical phases of increasing refractoriness to therapy: chronic phase (median duration 4-5 years), accelerated phase (median duration about one year), and blast crisis (median duration 3-6 months). During the chronic phase of the disease, myeloid cells containing Bcr-Abl retain the capacity to differentiate normally. Accelerated phase is an intermediate stage where patients show signs of disease progression. Eventually, there is progressive loss of the capacity for terminal differentiation resulting in disease progression to blast crisis (effectively an acute leukemia) which can be either of myeloid or lymphoid morphology.

Cytogenetic analysis is the gold standard diagnostic test in CML. However, in 10% of patients with CML, Philadelphia positivity cannot be demonstrated by cytogenic studies. Molecular analysis can detect BCR-ABL rearrangements in up to one half of these patients.

CML patients in myeloid blast crisis pose a major management challenge. Although a number of regimens have been studied including induction therapies for acute myeloid leukemia (AML) and hematopoietic stem cell transplantation, there is no standard therapy for these patients. Long-term survival rates of 5-10% have been reported following allogeneic transplantation. Poor responses have been reported for AML-like induction regimes as first line therapy.

Chronic leukemias are rare in childhood. The most common type, CML, accounts for less than 5% of all childhood leukemias. Although CML has been diagnosed in infants as young as 3 months, more than 80% of pediatric cases of CML are diagnosed after 4 years and 60% after age 6 years.

The cytogenetic hallmark of CML in children is similar to the adult population – a specific chromosomal translocation known as the Philadelphia (Ph) chromosome. The presence of this anomaly resulted in the fusion of the Abl proto-oncogene to the BCR gene resulting in the

production of an activated form of the Abl protein-tyrosine. Formation of BCR-ABL fusion oncogene has an inportant role in regulation of the cell growth. Insertion of the BCR-ABL gene into murine stem cells induces leukemia-like disease in mice.

Although characteristic of CML, Ph chromosome is not exclusive to it. This chromosomal abnormality is found in approximately 3% to 10% of childhood acute leukemias. These Ph+ acute leukemias are clinically indistinguishable from other acute leukemias except for a relatively poorer prognosis.

As in adult patients, the natural history of CML in pediatric patients divided into chronic, accelerated, and blast phases, representing progressive shift from the hyperproliferation of the mature cells to a differentiation arrest, with production of predominantly immature cells (blasts).

Recent advances in the management of CML have improved median survival to approximately 6 years (previously 3 to 4 years) with 35% to 40% of patients surviving 7 to 8 years. Because patients generally die within months of transformation to accelerated or blast phase, the major determinant if survival is the duration of the chronic phase, which can be variable.

The standard treatments for CML are allogenic bone marrow transplant (BMT) and interferon alpha (IFN-α). Transplants from HLA-identical sibling donors produce long-term disease survival in about 60% of patients who undergo BMT during the first chronic phase. Early mortality is between 10% and 30%.

IFN-α therapy can be started shortly after diagnosis. It produces major cytogenetic remissions in only 20% to 50% if pediatric patients. Toxicities of IFN-α (fever, anorexia, liver dysfunction) are common.

Imatinib (Gleevec, Novartis, Basel, Switzerland), formerly referred to as STI571 and CGP 57148B, is an inhibitor of specific protein tyrosine kinases that were targeted to the platelet-derived growth factor (PDGF) receptor. It was developed in a search for a selective kinase inhibitor of the constitutively active fusion product abl kinase. Imatinib was shown to block proliferation and induces apoptosis of Bcr-Abl-expressing CML and acute lymphocytic leukemia cell lines.

In clinical studies, imatinib was relatively well tolerated, side effects were usually mild to moderate in severity and most frequently included nausea, vomiting, diarrhea, edema, muscle cramps, hemorrhage, musculoskeletal pain, skin rash and peripheral edema.

Imatinib was approved by the Food and Drug Administration in May 2001 for the treatment of CML in chronic phase after failure of interferon-alpha, accelerated phase, and blast crisis based on response rates from single arm studies. In February 2002 Gleevec was approved for the treatment of gastrointestinal stromal tumors.

Clinical Review Section

## A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

**Established Name:** imatinib mesylate

**Proprietary Name:** Gleevec™

**Applicant:** Novartis Pharmaceuticals Corporation 59 Route 10 East Hanover, New Jersey 07936-1080

**Drug class:** Antineoplastic

**Indication:**
Current: Gleevec (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and objective response rate in GIST. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Proposed: Gleevec™ (imatinib mesylate) is indicated for the treatment of pediatric patients with Ph+ chronic phase CML who have recurred after stem cell transplant or are resistant to interferon alpha therapy.

## B. State of Armamentarium for Indication (s)

Single-agent chemotherapy with busulfan (**MYLERAN®** ) or hydroxyurea (**MYLOCEL™** ) has traditionally been the standard approach to the chronic phase of CML in children. These two agents, however, are not approved by the FDA for use children with CML.

The only approved product for the treatment of adult and pediatric patients with CML, is **ROFERON®-A (Interferon alfa-2a, recombinant).** Roferon-A is indicated for the treatment of ... chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

*Pediatric Use:* Use of Roferon-A in children with Ph-positive adult-type CML is supported by evidence from adequate and well-controlled studies of Roferon-A in adults with additional data from the literature on the use of alpha interferon in children with CML. A published report on 15 children with Ph-positive adult-type CML suggests a safety profile similar to that seen in adult CML; clinical responses were also observed

**GLEEVEC™ (imatinib mesylate)** is approved by the FDA for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

## C. Important Milestones in Product Development

May 1996 Drucker, *et. al.* publish report on a 2-phenylaminopyrimidine BCR ABL tyrosine kinase inhibitor with ability to suppress the growth of BCR-ABL positive cells

April 1998 IND 55,666:
A phase I, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles, and to evaluate for preliminary anti-leukemic effects of CBP 57148B in patients with chronic myeloid leukemia who are resistant to interferon-alpha.

September 2000: FDA issued a formal Written Request to Novartis to submit the dose finding study, including evaluation of pharmacokinetics, with MTD determined for all appropriate age groups (Phase 1 Study), and to determine STI571 activity in pediatric patients with Ph+ leukemia (Phase 2 Study).

September 2001: IND 55, 666:
A Phase 2 Study of STI571 in children with Ph+CML. The Study Design Section stated that " STI571 will be administered orally at 340mg/m2 (rounded to the nearest 100 mg) once daily". Reviewer commented that " The selected dose of 340 mg/m2 is based on limited data from the phase 1 study in children with Ph+ leukemia. The complete PK data from the phase 1 study and the rationale for the final dose selected for this phase 2 study should be submitted when available."

May 10, 2001: Gleevec™ (imatinib mesylate) was granted marketing approval in the UnitedStates (NDA 21-335) for treatment of adult patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Approval was based on response rates in single arm trials.

August 14, 2002: Sponsor presented sNDA data from study 106 to the Oncology Division. 45 day filing meeting. At this meeting the sponsor also presented the preliminary data from the pediatric phase 1 study 0103, which suggested that "the drug exposure observed at dose levels of 260 mg/m2/day and 340 mg/m2/day in children are similar to the exposure seen in adults treated at 400 mg and 600 mg daily (measured by plasma AUC), and are associated with a safety profile similar if not better than in adult trials and an efficacy similar to adult CML trials."

At this meeting FDA expressed concerns that using the 100 mg capsule size of Gleevec in pediatric patients would require rounding to the nearest 100 mg based on the calculated per m2 dose. FDA suggested use of 50 mg capsules to ensure appropriate dosing and safety due to rounding.

November 12, 2002: Novartis provided a formal response to the FAX sent by the FDA concerning the current plans for marketing the 50 mg capsules. The sponsor stated that "There are no plans for marketing the 50 mg capsules. A new NDA is planned to be submitted in December 2002 to provide for 100 mg and 400 mg tablets, which is intended to replace the 100 mg capsule dosage form. The 100 mg tablet is scored to allow for 50 mg dosing."

December 12, 2002: At the teleconference with Novartis the FDA notified Novartis that Gleevec will be granted approval under the Subpart H (Accelerated Approval) for the treatment of pediatric patients with Ph+ CML chronic phase, if the terms proposed by FDA are met. They included: (1) Submission of a chemistry supplement for a scored 100 mg tablet; (2) A Phase 4 commitment to complete and submit a Phase 2 study of the 260 mg/m2 dose of Gleevec administered to children with Ph+ CML chronic phase; (3) Labeling revisions.

## D. Other Relevant Information

Gleevec is approved in the US for the following indications:
(1) Gleevec is indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML), in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. (2) Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal tumors (GIST).

In this application the sponsor is seeking an approval of Gleevec for the treatment of pediatric patients with Ph+ chronic phase CML who have recurred after stem cell transplant or are resistant to interferon-alpha therapy.

## E. Important Issues with Pharmacologically Related Agents

Receptor tyrosine kinases (RTKs), such as the PDGF-R, bcr-abl, epidermal growth factor receptor, and insulin-like growth factor receptors, are expressed in a variety of tumos. The RTC is activated when the appropriate growth factor (ligand) binds extracellular portions of the receptor. Stimulation of these signal transduction pathways tend to cause cell proliferation, and inhibition tends to cause inhibition of proliferation. This finding has led to the development of a variety of tyrosine kinase inhibitors for the treatment of malignancy.

Gleevec was the first specific biochemical tyrosine kinase inhibitor to achieve marketing approval in the US. However, there are numerous receptor kinase signaling protein inhibitors in clinical oncology trials with a variety of specific molecular targets and disease activities. Heceptin is a monoclonal antibody targeting the HER2 neu tyrosine kinase receptor with activity and marketing approval in breast cancer. Iressa is an epidermal growth factor tyrosine kinase inhibitor with activity in lung cancer. SU101 is an isoxazole derivative that inhibits the platelet-derived growth factor receptor (PDGF-R)/Flk-1 family of receptor tyrosine kinases. These products have variable specificity for a particular receptor, and, in the case of Gleevec, the presence of a similar receptor to the bcr-abl tyrosine kinase expressed in CML, on a different tumor, the gastrointestinal stromal tumor (GIST), resulted in marked antitumor activity and eventually led to marketing approval in two very different specific malignancies: CML and GIST.

These agents are theoretically less toxic than the cytotoxic agents, therefore the paradigm of dose escalation until the maximum tolerated dose may not be appropriate in these agents. Toxicity may be relatively mild, and well tolerated, as in the hematologic toxicities seen with Gleevec, which rarely resulted in the development of infections.

## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Gleevec is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. No new information with regard to chemistry, toxicology and microbiology was submitted with this NDA. This review is a combined medical and statistical review. Please see biopharmaceutical review below.

## III. Human Pharmacokinetics and Pharmacodynamics

### A. Pharmacokinetics

Pediatric Pharmacokinetics:

Pharmacokinetic studies were performed in 27 of the 31 patients enrolled in Study 103. Results show that the PK in children are similar to the PK in adults. Absorption was rapid, with a Cmax of 2-4 hours. Clearance of Gleevec was similar to adult values as well, with an apparent oral clearance of 11.0 L/h/m2 (children) vs 10.0 L/h/m2 (adult). The mean half-life in children was 14.8 hr, whereas in adults it was 17.1 hours. There was poor dose-proportionality, in other words an increase in dose did not produce a proportional change in exposure (AUC). There was considerable overlap in AUC between the 260 and 340 mg/m2 doses, and both were similar to the AUC from the 400 mg dose in adults. There was accumulation with chronic dosing, with an accumulation factor of 1.5 and 2.2 at the 260 and 340 mg/m2 dose levels, respectively.

Drug-Drug Interactions:

Gleevec is metabolized primarily by CYP3A4 isozymes. Drugs which induce these enzymes would be expected to induce the metabolism of Gleevec. The sponsor submitted a study in healthy volunteers to explore such a possible drug interaction. Rifampin, a potent inducer of the CYP3A4 isozymes, was administered for 11 days; Gleevec PK studies were done before and after rifampin administration. Results showed that rifampin increased Gleevec clearance four-fold, and decreased area under the curve by approximately the same amount. The clinical significance is that patients who receive the recommended dose of Gleevec along with a potent CYP3A4 inducer will likely have a poorer clinical response.

### B. Pharmacodynamics

No relationship was demonstrated between pharmacokinetics and pharmacodynamics.

## IV. Description of Clinical Data and Sources

### A. Overall Data

The primary source for this sNDA review consisted of data submitted to the sNDA 21-335/S-003 on Study 0103 and Study 03001 in pediatric patients with Ph+CML and Ph+ acute leukemias. Additional information was gained from the literature sources cited in the Literature Review Section.

### B. Tables Listing the Clinical Trials

**Table 1: Clinical Trials**

| Study Number | Patient exposure | Diagnosis | | | |
|---|---|---|---|---|---|
| | | CML chronic phase | Blast crisis | AML | ALL |
| **0103** | 31 | 14 | 1 | 7 | 9 |
| **03001** | 8 | 3 | 1 | 0 | 4 |

### C. Postmarketing Experience

Gleevec was approved on May 10, 2001. As of November 11, 2002, postmarketing surveillance has subsequently received 818 adverse event reports. It should be noted that many of these reports were duplicated.

**Table 2: Most common adverse events (>5%) reported to FDA (N= 818)**

| Preferred term | N | % of total |
|---|---|---|
| Pyrexia | 106 | 13 |
| Pancytopenia | 75 | 9.2 |
| Nausea | 63 | 7.7 |
| Thrombocytopenia | 58 | 7.1 |
| Vomiting | 54 | 6.6 |
| Neutropenia | 49 | 6.0 |
| Dyspnea NOS | 45 | 5.5 |
| Oedema NOS | 43 | 5.3 |
| Pneumonia NOS | 43 | 5.0 |

In addition, there were 59 reports of renal failure or impairment; including 14 reports of dialysis. There were 91 reports of bilirubin or transaminase abnormalities, 15 reports of hepatotoxicity, and 6 reports of hepatic failure. There were 26 reports of sepsis and 5 reports of shock. There were 18 reports of rash, 17 reports of erythema multiforme, and 7 reports each of Stevens Johnson syndrome and toxicoderma. There were 118 reports of various types of edema, including 4 reports of cerebral edema and 4 reports of papilledema. Clearly this drug causes renal and hepatic toxicity in a minority of patients, rash and edema is fairly common, and severe skin reactions and cerebral edema have been reported. A review is currently in progress to eliminate duplicate reports and to identify emerging patterns of adverse events.

### D. Literature Review

The sponsor performed an extensive review of the literature of treatment of CML in adult and pediatric patients and provided copies of these references (NDA 21-335/S-003, v. 14). The FDA medical reviewer performed an additional literature review with attention to the more recent publications about treatment of CML in children. The references cited are listed at the end of the NDA review. The sponsor's literature review appears to be adequate.

## V. Clinical Review Methods

### A. How the Review was Conducted

The review centers on the data from two Phase 1 studies (Study 0103 and Study 03001), which was the only primary data submitted in this supplemental NDA. Data on a total of 39 children with Ph+ CML chronic phase and Ph+ acute leukemias were considered sufficient for an efficacy

conclusion. Support for the efficacy data of Gleevec in children is mainly extrapolated from adults with Ph+ CML.

The medical review of this NDA 21-335/S-003 included:

- Initial submission of protocols for the two studies
- Protocol amendments
- The following documents from the NDA submission:

| | |
|---|---|
| Item 1 | Index |
| Item 2 | Labeling |
| Item 3 | Application Summary |
| Item 4 and 5 | Chemistry, Manufacturing and Controls and Nonclinical Pharmacology and Toxicology Section (Cross-reference NDA 21-335) |
| Item 6 | Human Pharmacokinetics and Bioavailability |
| Item 7 | Microbiology N/A |
| Item 8 | Clinical Data |
| Item 9 | Safety update N/A |
| Item 10 | Statistical Section |

The following sNDA components were submitted in electronic form for Study 0103:

Labeling
Case Report Tabulation
Case Report Forms

- Patients listings (electronic) for the Study 0103, which were subject of queries in JUMP and MS Access
- Statistical review included analyses using the SAS datasets

### B. Overview of Materials Consulted in Review

Data submitted under sNDA 21-355/S-003 included primary datasets from two Phase 1 studies, clinical reports from the Phase 1 studies, labeling, and communications with the sponsor. In addition, the concept of extrapolation of efficacy results from the adult trials if the disease is considered the same in the adult and in children, was discussed at the Oncology Drugs Advisory Committee (ODAC).

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

The primary data was analyzed for consistency with the study reports and with selected patient narratives. DSI audit was not conducted.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The studies were conducted under US IND 55,666 in full compliance with the principles of the Declaration of Helsinki, including all current amendments, or with the laws and regulations of the country in which the studies were conducted. Prior to initiation of the studies, the protocols, and the patient informed consent were reviewed and approved by the ethics committees or institutional review boards of the centers of the study. Subsequent protocols amendments were also submitted, reviewed and approved before implementation.

### E. Evaluation of Financial Disclosure

A completed Financial Disclosure (FD) FDA Form 3454 is submitted with attached list of principal investigators. Information regarding the FD was properly collected by Novartis. Information was obtained through the Children Oncology Group which released information on all principal investigators.

In summary: No principal investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the investigators from US and non-US centers participating in this trials.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

Study 0103 and Study 03001 were open-label, multicenter, phase 1 dose-finding studies in children with Ph+ CML and Ph+ acute leukemias recurrent after stem cell transplant or resistant to interferon-alpha therapy or multi-drug regimens. Study 0103 in 31 pediatric patients was conducted by the National Cancer Institute, Children's Oncology Group (NCI/COG) and supported by Novartis. Additional data were submitted from eight pediatric patients with Ph+ leukemias in Study 03001, also supported by Novartis.

The primary objectives for each study were evaluation of pharmacokinetics with MTD determined for all appropriate age groups and safety profile assessment. The secondary objectives included evaluation of the anti-leukemic effect of Gleevec in pediatric patients with Ph+ leukemias.

Pharmacokinetic results in 27 children showed pharmacokinetics parameters to be similar to the adult values. There was poor dose proportionality in children. The MTD remains undefined and appears to be > 570 mg/m2.

The analysis of the secondary endpoint, anti-leukemic effect of Gleevec, showed that Gleevec produced major and complete cytogenetic responses in 13 of 16 evaluable children with Ph+ CML chronic phase across all tested dose levels. At the recommended dose of 260 mg/m2/day, 4 of 6 patients achieved a complete cytogenetic response. Support for the efficacy of Gleevec in

children mainly comes from extrapolation of efficacy in adults with Ph+ CML. The cytogenetic responses in children confirm that efficacy in children is similar to adults.

### B. General Approach to Review of the Efficacy of the Drug

This review focused on the supplemental NDA data submitted by Novartis on 31 pediatric patients (Study 0103) and on 8 pediatric patients (Study 03001) with Philadelphia-chromosome positive CML in chronic phase and Ph+ acute leukemias recurrent after the stem cell transplant or after the interferon-alpha therapy or multi-drugs regimens. Submitted study reports and primary data for each patient were reviewed.

### C. Detailed Review of Trials by Indication

The primary objectives for both studies (Study 0103 and Study 03001) were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of Gleevec in children with recurrent or refractory Philadelphia chromosome-positive (Ph+) leukemia; and to characterize the pharmacokinetic (PK) behavior of Gleevec in this patient population. The secondary objective was to assess the anti-leukemic activity of Gleevec.

**Study 0103: Efficacy summary for patients with Ph+ chronic phase CML.**

Eligible chronic phase Ph+ CML patients were either recurrent after stem cell transplantation or resistant to IFN-alpha therapy.

A total of fifteen patients in chronic phase CML were treated with Gleevec at the following daily doses: 260 mg/m2 – 3 patients, 340 mg/m2 – 5 patients, 440 mg/m2 – 5 patients and 2 patients were treated with 570 mg/m2. One patient treated with 340 mg/m2 relapsed and one patient treated with the 260 mg/m2 had disease progression without prior response to Gleevec.

Reviewer Table 3 presents the FDA efficacy summary of cytogenetic response (confirmed and unconfirmed) for chronic phase CML patients.

The sponsor provided the following efficacy parameter definitions:

Cytogenetic response:
1. Complete (0% Ph-positive cells)
2. Partial (1-35%)
3. Minor (36-65%)
4. Minimal (66-95%)
5. None (96-100%)

Major cytogenetic response (MCyR) was defined as the sum of:
- Complete cytogenetic response (CCyR) (if patients had 0% Ph+ cells at least once), and

- Partial cytogenetic response (PCyR) (if patients had ≤ 35% Ph+ cells at least once).

Confirmed cytogenetic response: cytogenetic responses confirmed by repeat exam at least 1 month later.

**Table 3: FDA Efficacy Summary of Cytogenetic Response for Ph+ Chronic Phase CML Patients (study 0103)**

| | 260 mg/m$^2$ | 340 mg/m$^2$ | 440 mg/m$^2$ | 570 mg/m$^2$ | Total |
|---|---|---|---|---|---|
| **NUMBER OF PATIENTS TREATED** | 3 | 4 | 5 | 2 | 14 |
| **Best Response** | | | | | |
| Complete | 2 | 2 | 2 | 1 | 7 |
| Partial | 0 | 1 | 3 | 0 | 4 |
| Minor | 0 | 0 | 0 | 1 | 1 |
| Minimal | 1 | 0 | 0 | 0 | 1 |
| None | 0 | 0 | 0 | 0 | 0 |
| Not done | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 1 | 0 | 0 | 1 |

In 13 patients with CML for whom cytogenetic data are available, 11 (85%; 95% CI 56-98%) achieved a major cytogenic response with 7 achieving a complete cytogenic response. Eight of 11 cytogenetic responses were confirmed by repeat exam at least 1 month later.

Two of three patients with chronic phase CML who achieved CcyR were treated at the sponsor's proposed marketing dose of 260 mg/m2/day.

***Clinical Reviewer Comment:*** *In this group of patients age ranged from 8 to 20 years, with a mean of 15.2 years. Two of three patients achieved complete cytogenetic remission (CCyR) at the sponsor's proposed marketing dose of 260 mg/m2 and were in the age group between 12 and 18 years old. Only one of the two patients (1006) had a confirmed cytogenetic response.*

***Statistical Reviewer Comment:*** *From this reviewer's assessments there were eight confirmed complete and major cytogenetic responses among all the patients with CML chronic phase. One of these patients had a response duration of 146 days. The other seven patients with confirmed cytogenetic responses had censored response durations days of 25, 28, 125, 147, 412, 452, and 477.*

***Clinical Reviewer Comment:*** *The sponsor indicated that "peripheral neutrophil and blast counts are not available for any patients and therefore it is not possible to assess hematologic response including assessment of the peripheral blood" (Clinical Study Report, v.8, p.28, Section 6.1.5.).*

For chronic phase CML patients, the sponsor estimated 12 months survival (and also 18 months survival) as 93% with corresponding 95% C.I. as 80.7%-100%.

***Statistical Reviewer Comment:***

*1. The confidence interval, 80.7%-100%, presented by the sponsor here is based on normal theory. This is not an appropriate way of constructing confidence intervals in this setting, since the sample size and number of events are small (also the estimate is far away from 0.5). More appropriate methods of constructing 95% confidence intervals here give for both treatment arms lower limits and upper limits smaller than those presented by the sponsor.*

*The Kaplan-Meier estimator of 12-month (18-month) survival is less than or equal to one minus the fraction of all observations that are events prior to 12 months (18 months). Here, one minus the fraction of all observations that are events prior to 12 months (18 months) is 1-1/15=14/15 = 93.3%. The corresponding 95% CI (exact CI) is 68.1% to 99.8%. Thus, a 95% CI for 12-month (18-month) survival (calculated by appropriate means) has to be "less than" 68.1% to 99.8%.*

2. *These comments also apply to "95% confidence intervals" for 6-month, 9-month and one-year survival rates for initial dose groups for each of chronic phase patients and acute phase patients. These confidence intervals are far from correct. For example for the 260 mg/m$^2$ subgroup for the CML chronic phase patients the 95% CI for one-year survival given by the sponsor is 100% to 100%. Three CML chronic phase patients were initially given 260 mg/m$^2$ of Gleevec. All three patients have survival times beyond 20 months. If the design was to have exactly three patients initially given 260 mg/m$^2$ of Gleevec and to follow these patients at least 12 months, then the 95% CI for one-year survival would be 29.4% to 100%.*

Reviewer Table 4 presents the FDA efficacy summary of cytogenetic response for patients with acute phase leukemia.

**Table 4: FDA Efficacy Summary of Cytogenetic Response for Patients with Ph+ Acute Leukemia (study 0103)**

| | 260 mg/m$^2$ | 340 mg/m$^2$ | 440 mg/m$^2$ | 570 mg/m$^2$ | Total |
|---|---|---|---|---|---|
| **NUMBER OF PATIENTS TREATED** | 3 | 6 | 3 | 4 | 16 |
| **Best Response** | | | | | |
| Complete | 1 | 2 | 2 | 1 | 6 |
| Partial | 0 | 1 | 0 | 2 | 3 |
| Minor | 0 | 0 | 0 | 0 | 0 |
| Minimal | 1 | 1 | 1 | 0 | 3 |
| None | 1 | 0 | 0 | 0 | 1 |
| Not done | 0 | 2 | 0 | 1 | 3 |
| Missing | 0 | 0 | 0 | 0 | 0 |

Eligible patients had AML, ALL or CML in blast crisis. Among the sixteen patients in acute phase, three patients were treated daily with 260 mg/m$^2$, six patients received 340 mg/m$^2$, three patients were treated with 440 mg/m$^2$, and four patients were treated with 570 mg/m$^2$. Overall, seven patients (one on

260 mg/m$^2$, one on 340 mg/m$^2$, two on 440 mg/m$^2$, and three on 570 mg/m$^2$) relapsed and four patients progressed without responding (two on 260 mg/m$^2$ and two on 340 mg/m$^2$).

***Clinical Reviewer Comment:*** *In this group of patients age ranged from 3 to 18, with a mean of 9.5 years. A total of 9 (56%: 95% CI 29.9-80.2%) patients achieved major cytogenetic response and 6 of these patients had a complete response. Five of the complete or major cytogenetic responses were confirmed by repeated exam at least 1 month later.*

*Only 2 of 6 patients treated at the sponsor's proposed marketing dose of 340 mg/m2 achieved CCyR. One of these 2 patients had confirmed cytogenetic response.*

***Statistical Reviewer Comment:*** *From this reviewer's assessments there were five confirmed complete or major cytogenetic responses among patients with acute leukemia. These five patients had censored MCyR durations in days of 28, 29, 51, 58, and 63. The remaining responses were not confirmed.*

For acute phase patients, the sponsor estimated 12 months survival as 40.9% with corresponding 95% C.I. as 13.4%-68.5%.

***Statistical Reviewer Comment:*** *The confidence interval, 13.4%-68.5%, presented by the sponsor here is based on normal theory. This is not an appropriate way of constructing confidence intervals in this setting, since the sample size and number of events are small. From this reviewer's calculations using the survival data that the sponsor submitted (pages 8-125 to 8-128), the Kaplan-Meier estimate for 12-month survival for acute phase patients is 43.8%. This estimate involves eight events at or before 8 months and 2 censored values prior to 8 months (there were no events between 8 and 12 months and 4 censored values inclusively between 8 and 12 months). There is less information here about the one-year survival rate than there would have been if all patients were followed for at least 12 months and there were nine events (survival times) prior to 12 months. In this situation the estimated one-year survival rate would be 7/16 = 43.8% with corresponding 95% CI (exact CI) of 19.8% to 70.1%. Thus, the 95% CI associated with the Kaplan-Meier estimate for 12-month survival for acute phase patients of 43.8% must contain (be wider than) the interval from 19.8% to 70.1%.*

As stated in Section 6.1.5, of the Clinical Study Report "peripheral blood neutrophils and blast counts are not available and therefore it is not possible to assess hematological response including an assessment of the peripheral blood. In addition, the percentage of promyelocytes in the bone marrow is not available and therefore the assessment of bone marrow response in acute phase patients with myeloid phenotype can be based only on the percentage of bone marrow blasts."

Reviewer Table 5 below presents the summary of bone marrow responses in patients with acute leukemia based only on the percentage of bone marrow blasts.

**Table 5: Bone Marrow Responses in Patients with Ph+ Acute Leukemia**

| Bone marrow response | Myeloid phenotype (n=6) | Lymphoid phenotype (n=9) | All (n=15) |
|---|---|---|---|
| M1 (0-5%) blasts in count | 3 (50%) | 6 (67%) | 9 (60%) |
| M2 (>5-25%) | | 1 (11%) | 1 (7%) |
| M3 (>25% blasts) | 3 (50%) | 2 (22%) | 5 (33%) |

The majority of bone marrow responses (60%) in patients with acute leukemia were classified by the sponsor as M1, followed by M3 and M2 (33% and 7%, respectively).

**Study 03001: Efficacy summary for patients with Ph+ chronic phase CML resistant or intolerant to IFN and patients with Ph+ acute leukemia.**

A total of 8 pediatric patients age 5 to 17 were enrolled in this study. Three patients had chronic phase CML, four patients had Ph+ALL and one patient had CML in lymphoid blast crisis.

***Reviewer Comment:*** *In the group of 3 patients with CML chronic phase, complete cytogenetic response was achieved in 2 patients (ID 01/53 and ID 01/38, dose level 242 mg/m2 and 257 mg/m2, respectively). Both patients had confirmed responses. These two complete cytogenetic responses were continuing at last evaluation at 395 and 389 days.*

*All of the 3 patients with CML chronic phase achieved complete hematologic response ranging from 364 to 564 days. Two of the three patients remain in continuous hematologic remission (Source: Clinical Study Report, v.11, p. 13).*

*Only 1 of 5 patients with acute leukemia had a complete cytogenetic response. This patient (ID 01/25) went off study at day 79.*

## D. Efficacy Conclusions

In 2 Phase 1 studies in a total of 16 children with Ph+ CML in chronic phase evaluable for cytogenetic response, Gleevec induced an 81% (13/16) cytogenetic response rate with 10/13 (77%) confirmed by repeat exam at least 1 month later. Five of the confirmed cytogenetic responses were ongoing at well over a year (maximum 590 days).

In 2 Phase 1 studies in a total of 21 patients with Ph+ acute leukemia treated with Gleevec the cytogenetic response rate was 48% (10/21). Five of the 10 cytogenetic responses were confirmed Confirmed cytogenetic responses were ongoing at 28, 29, 51, 58, and 63 days. Median duration of survival in study 0103 was 8 months with 7 of 16 patients still alive. Survival data is not reported for study 03001.

In conclusion the cytogenetic response rate in children with Ph+ CML in chronic phase recurrent after stem cell transplant or resistant to interferon alpha is consistent with and is strongly supported by the results in adult patients. Gleevec is approved under Subpart H for Ph+ CML in adults in chronic phase resistant or intolerant to interferon alpha, in accelerated phase and in blast crisis, based on hematologic response rate and cytogenetic response rate. There is adequate information to support the Applicant's proposed dose.

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

Gleevec safety has been demonstrated in 39 children with Ph+ CML chronic phase and Ph+ acute leukemias (31 patients in Study 0103 and 8 patients in Study 03001). The safety data on Gleevec available from the adult trials showed that Gleevec has substantially less severe adverse effects than the present standard treatment (Alpha Interferon with or without Ara-C). The most common adverse effects observed in pediatric patients at the recommended dose of 260 mg/m2/day (10 patients total) are nausea (83%), vomiting (83%), pyrexia (50%), diarrhea (33%), headache (33%), hypotension (33%), fatigue (33%), and stomatitis (33%).

In all patients in both studies Grade 3/4 hematologic toxicities including neutropenia, thrombocytopenia and anemia, occurred in 50 %, 50%, and 30%, respectively. Electrolyte abnormalities, such as hypokalemia, hyperglycemia, hypercalcemia, and hypophosphatemia occurred in 16% of all patients. Grade 3/4 elevated SGOT was reported in 16% of all cases.

In conclusion: Gleevec safety profile is adequate for marketing approval for use in children with Ph+ CML chronic phase recurrent after stem cell transplant or resistant to interferon-alpha therapy.

### B. Description of Patient Exposure

The safety review is conducted using the electronic database from the Phase 1 Dose-escalating study (Study 0103) of Gleevec given to patients with Ph+ CML chronic phase and Ph+ acute leukemias. The safety review for the second Phase 1 study (03001) is based on the analysis of data submitted by the sponsor in sNDA 21-335/S-003, Volumes 11, 12, and 15.

A total of 39 children with Ph+ CML chronic phase or acute Ph+ ALL or AML (31 and 8 for the Study 0103 and Study 03001, respectively) were treated with Gleevec. The patient population consisted of children and young adults recurrent either after stem cell transplantation or interferon-alpha therapy (IFN).

***Reviewer Comment:*** *Differences between the two protocols for Study 0103 and Study 01001, as well as safety and efficacy analysis, will be outlined by the reviewer after each of the appropriate sections of the review.*

Patient Exposure in Study 0103.

The number of patients exposed to study drug in each cohort by disease group is presented in the sponsor's Table 4-6 (v.2, p. 20)

**Table 6: Number (%) of patients in each dose cohort by disease group (study 0103) Ref: Sponsor's Table 4-6**

| | CML Chronic phase n (%) | Acute phase n (%) | All patients n (%) |
|---|---|---|---|
| Total no. of patients treated | 15 (100) | 16 (100) | 31 (100) |
| Dose cohort (mg/m2)* | | | |
| 260 | 3 (20.0) | 3 (18.8 ) | 6 (19.4) |
| 340 | 5 (33.3) | 6 (37.5) | 11 (35.5) |
| 440 | 5 (33.3) | 3 (18.8) | 8 (25.8) |
| 570 | 2 (13.3) | 4 (25.0) | 6 (19.4) |

*mg/m2 rounded to the nearest 50mg increment

Thirty one children and young adults with recurrent or refractory Ph+ CML, ALL or AML received Gleevec in this Phase I study. Patients ≤21.99 years of age were treated at one of the 4 dose levels, starting at 260 mg/m2 (dose level 1) and escalated to 570 mg/m2 (dose level 4). As stated by the sponsor in the Clinical Data Section, v.7, p.36 "Sixteen patients were on therapy for at least six months, and eight (two per dose cohort) for at least 12 months. The median duration of exposure was 504 days in chronic CML and 60.5 days in the acute phase patients." Overall, the median duration of treatment was 188 days, ranging from 1 to 24.8 months.

***Reviewer Comment:*** *In this study a total of 14 were diagnosed with Ph+ CML, 9 had AML, 7 patients were diagnosed with ALL, and 1 patient had confirmed blast crisis (patient 1026 with extramedullary blast crisis, which manifested with cell infiltration of the testes, was classified by the sponsor as "chronic phase CML").*

Twenty eight daily doses of Gleevec constitute one course. Two courses were given in the absence of progressive disease. Patients who did not show drug related toxicities were continued on therapy.

Patient Exposure in Study 03001.

Patients exposure to Gleevec is presented in the Clinical Study Report.

**Table 7: Patient exposure to ST1571**

| Patient | Disease group | Age in Years | BSA[a] | mg/m$^2$ | Initial dose/day |
|---|---|---|---|---|---|
| 01/24 | CML | 5 | 0.750 | 200.000 | 150 |
| 01/38 | CML | 13 | 1.650 | 257.576 | 425 |
| 01/53 | CML | 11 | 0.930 | 241.935 | 225 |
| 01/25 | ALL | 5 | 0.720 | 173.611 | 125 |
| 01/31 | ALL | 11 | 1.210 | 185.950 | 225 |
| 01/44 | ALL | 5 | 0.790 | 253.165 | 200 |
| 01/48 | ALL | 17 | 1.660 | 256.024 | 425 |
| 01/50 | Lymphoid blast | 7 | 0 | .690 | 250 |

*Source: Modified from Sponsor's Post-text listings 7.1-1 and 10.4-1)*

***Reviewer Comment:*** *In the Clinical Study Report, the sponsor also provided data for the duration of exposure to Gleevec. Mean exposure to Gleevec was 313.5 days, range from 48 to 675 days. (Ref: Post-text Table 8.1-2 and post-text listing 8.1-1).*

## D. Methods and Specific Findings of Safety Review

The safety review is conducted using the electronic database from the Study 0103 and for both Study 0103 and Study 03001 Volumes 8, 9, 11, 12, and 15 of the sNDA 21-335/S-003. Thirty nine pediatric patients with Ph+ CML chronic phase and Ph+ acute leukemias recurred after stem cell transplant or resistant to interferon-alpha were treated with Gleevec in these studies.

## E. Adequacy of Safety Testing

The safety assessment appears adequate and was carried out on all 39 patients and included extent of exposure, deaths during the study, deaths within the first 28 days after discontinuation of the study drug, discontinuation due to Adverse Events, SAE's and AE's. Grade 3 or 4 laboratory abnormalities listed as AE's were used to summarize laboratory abnormalities.

During Course 1 patients were evaluated weekly (physical exam, pharmacokinetics, and main biochemichal parameters, such as electrolytes level and LFT's). Complete blood count (CBC) with differential was done three time during the each week of the course.

During the Course 2 physical exam was performed once at the beginning of the course, with weekly assessment of electrolytes and LFT's. During the subsequent courses only CBC with differential was repeated weekly, while the rest of the evaluation occurred at the beginning of each new 28-Day course. There were no specific areas that require further assessment because of unexpected toxicities or clinical findings.

## F. Summary of Critical Safety Findings and Limitations of Data

**1. Deaths on Study.**

Study 0103:
In the submission, v.7. p. 60, the sponsor stated that "a single acute phase patient died during the study due to progressive leukemia." Death occurred in the second (340mg/m2) dose cohort.

**Table 8: Reasons for Death During the Study and in the First 28 days of Discontinuing the Treatment**

| | Acute leukemia (N=6) | CML chronic phase (N=5) |
|---|---|---|
| **Dose level** (mg/m2) | 340 | 340 |
| **Death** | | |
| on study | X | |
| first 28 days | | X |
| **Cause of death** | | |
| Tumor and infection | X | |
| "other" | | X |
| **TOTAL** | **1 (6.3%)** | **1 (6.7%)** |

*Source: Modified from Sponsor's Post-text table 10.2-5, v. 9, p.269-272)*

Ref: "death Report Form" of CRF.

A total of 16 children with Ph+ acute leukemias and 15 children (1 had a lymphoid blast crisis) in the chronic phase of CML were treated in Study 0103. Among them a total of 6 and 5 patients with acute leukemias and in chronic phase, respectively received dose of 340mg/m2. Two patients (one in each phase) died either during the treatment or in the first 28 days after discontinuing the treatment.

***Reviewer Comment:*** *One patient (ID 1021) died from the acute leukemia while on Gleevec and one patient (ID 1026) with testicular relapse died in the chronic phase from the disease progression within 28 days of discontinuing Gleevec.*

Study 03001: One patient with ALL died while receiving Gleevec. No patient died in the first 28 days after discontinuing Gleevec.

***Reviewer Comment:*** *One patient (ID 0048) who had ALL died during the Cycle 2, Day 47 due to febrile neutropenia, Aspergillus pneumonia. Gleevec was continued until the patient's death.*

**3. Discontinuation due to Adverse Events.**
No patient discontinued due to study-drug-related AE's.

**4. Adverse Events (AE) and Serious Adverse Events (SAE) in Study 0103.**

The following Table shows the percent of patients with each adverse event for adverse events seen in ≥10% of patients, all severity grades with Ph+ CML chronic phase and Ph+ acute leukemias.

**Table 9: Number (%) of Patients with most frequent AEs overall by preferred term and disease group (≥10% in all Patients)**

| | Chronic Phase CML | Acute phase | All patients |
|---|---|---|---|
| Total no. of patients treated n (%) | 15 (100) | 16 (100) | 31 (100) |
| Total no. of patients with any AE | 15 (100) | 15 (93.8) | 30 (96.8) |
| Total no. of patients with any AE (excl. laboratory) | 14 (93.3) | 14 (87.5) | 28 (90.3) |
| **Adverse event** | | | |
| Vomiting NOS | 5 (33.3) | 9 (56.3) | 14 (45.2) |
| Nausea | 6 (40.0) | 3 (18.8) | 9 (29.0) |
| Diarrhea | 6 (40.0) | 2 (12.5) | 8 (25.8) |
| Infection NOS | 3 (20.0) | 5 (31.3) | 8 (25.8) |
| Pyrexia | 2 (13.3) | 6 (37.5) | 8 (25.8) |
| Febrile neutropenia | 2 (13.3) | 5 (31.3) | 7 (22.6) |
| Skin desquamation NOS | 4 (26.7) | 3 (18.8) | 7 (22.6) |
| Abdominal pain NOS | 4 (26.7) | 2 (12.5) | 6 (19.4) |
| Headache | 3 (20.0) | 2 (12.5) | 5 (16.1) |
| Hypotension NOS | 1 (6.7) | 4 (25.0) | 5 (16.1) |
| Pain NOS | 2 (13.3) | 3 (18.8) | 5 (16.1) |
| Catheter related infection | 0 | 4 (25.0) | 4 (12.9) |
| Cough | 2 (13.3) | 2 (12.5) | 4 (12.9) |
| Fatigue | 4 (26.7) | 0 | 4 (12.9) |
| Stomatitis | 3 (20.0) | 1 (6.3) | 4 (12.9) |

**Source: Post-text table 10.1-2 and Appendix 7.1 listing 10.1-1a**

*Reviewer Comment: Patients identified by the sponsor as "acute phase" are those who diagnosed with Ph+ acute leukemias (ALL or AML).*

The most commonly reported adverse events in CML chronic phase and acute leukemias were nausea, vomiting, diarrhea, infection, pyrexia, febrile neutroenia, fatigue, skin changes, and stomatitis.

In Table 10, the numbers and percentages of patients in Study0103 experiencing AEs are summarized by the dose cohort including the recommended dose level and one level above.

**Table 10: Number (%) of Patients with AEs by dose cohort (≥10% at any dose)**

| | 260 mg/m$^2$ | 340 mg/m$^2$ |
|---|---|---|
| Total no. of pats. treated n (%) | 6 (100) | 11 (100) |
| Total no. of pats. with any AE | 6 (100) | 11 (100) |
| Total no. of pats. with any AE (excl. laboratory) | 6 (100) | 11 (100) |
| **Adverse event** | | |
| Vomiting NOS | 5 (83.3) | 3 (27.3) |
| Nausea | 5 (83.3) | 1 (9.1) |
| Diarrhea | 2 (33.3) | 1 (9.1) |
| Infection NOS | 2 (33.3) | 4 (36.4) |
| Pyrexia | 3 (50.0) | 2 (18.2) |
| Febrile neutropenia | 0 | 3 (27.3) |
| Skin desquamation NOS | 1 (16.7) | 3 (27.3) |
| Abdominal pain NOS | 1 (16.7) | 2 (18.2) |
| Headache | 2 (33.3) | 1 (9.1) |
| Hypotension NOS | 2 (33.3) | 1 (9.1) |
| Pain NOS | 1 (16.7) | 3 (27.3) |
| Catheter related infection | 1 (16.7) | 1 (9.1) |
| Cough | 1 (16.7) | 1 (9.1) |
| Fatigue | 2 (33.3) | 1 (9.1) |
| Stomatitis | 2 (33.3) | 1 (9.1) |

**Modified from the sponsor's Post-text table 10.1-2 and Appendix 7.1 listing 10.1-1a**

The following Table of grade 3 or 4 non-hematologic adverse events in Study 0103 by dose cohort is modified from the Applicant's Study Report (Source: Post-text table 10.2-3 and Post-text listing 10.2-3)

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**Table 11: Number (%) of Patients with grade 3/4 non-hematologic toxicities**

| | 260 mg/m$^2$ | 340 mg/m$^2$ |
|---|---|---|
| Total no. of pats. treated n (%) | 6 (100) | 11 (100) |
| Total no. of pats. with any AE | 5 (83.3) | 10 (90.9) |
| Total no. of patients with any AE (excl. laboratory) | 4 (66.7) | 7 (63.6) |
| **Adverse event** | | |
| Infection NOS | 2 (33.3) | 4 (36.4) |
| Catheter related infection | 1 (16.7) | 1 (9.1) |
| Febrile neutropenia | 0 | 2 (18.2) |
| Pain NOS | 0 | 2 (18.2) |
| Peripheral motor neuropathy | 1 (16.7) | 0 |
| Hypotension NOS | 0 | 1 (9.1) |

Table below presents number of patients with grade 3/4 hematologic toxicities by dose cohort in Study 0103.

**Table 12: Number (%) of Patients with grade 3/4 Hematologic Toxicities**

| | 260 mg/m2 | 340 mg/m2 |
|---|---|---|
| Total no. of patients treated n (%) | 6 (100) | 11 (100) |
| Total no. of patients with any hematologic AE grade 3/4 | 5 (83.3) | 10 (90.9) |
| **Adverse event** | | |
| ANC | 3 (50.0) | 10 (90.9) |
| Hemoglobin | 2 (33.3) | 5 (45.5) |
| Platelets | 3 (50) | 5 (45.5) |
| WBC | 2 (33.3) | 5 (45.5) |

*Reviewer Comment: The incidence of grade 3/4 myelosuppression in chronic phase CML patients apears to be high. However, this can almost certainly be attributed to the approach to dose reduction in the face of myelosuppression that was applied in this current study. Thus, dose interruption was permitted only after the development of grade 4 neutropenia whereas in all adult studies treatment was withheld in the event of either grade 2 neutropenia or thrombocytopenia. Although 87% of chronic phase CML patients developed grade 3/4 hematologic toxicity in this current study, no severe episodes of febrile neutropenia or bleeding were reported in any of these patients.*

## VIII. Dosing, Regimen, and Administration

Study 0103 and Study 03001 were dose escalation trials that utilized a standard design for determining the MTD. Patient population included children with Ph+ leukemias recurrent after the stem cell transplant, resistant to interferon-alpha therapy or multi-drug regimens.

In the Study 0103 the starting dose of Gleevec of 260 mg/m2 daily was extrapolated from the efficacious dose of 400 mg in adults with Ph+ CML chronic phase. Dose levels for subsequent groups were escalated up to 570 mg/m2. The MTD remains undefined and appears to be > 570 mg/m2.

In a second study (03001) children were treated with Gleevec doses ranging from 173 to 362 mg/m2.

The recommended dose of Gleevec for pediatric patients with Ph+ CML chronic phase is 260 mg/m2/day administered orally as a once daily dose or alternatively the daily dose may be split into two – once in the morning and once in the evening.

Gleevec appears to be well-tolerated at doses up to 570 mg/m2 and there appears to be a wide therapeutic window, especially compared with cytotoxic agents.

## IX. Use in Special Populations

### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A total of 39 children with Ph+ CML chronic phase and Ph+ acute leukemias who have recurred after stem cell transplant or resistant to interferon alpha were treated with Gleevec on Study 0103 and Study 03001. Twenty nine (74%) of patients were males, and 10 (26%) were females.

We agree with the Applicant that there are insufficient numbers of patients to permit analyses.

### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

We agree with the Applicant that there are insufficient numbers of patients in each of the age group to permit analyses. This also applies to race and ethnicity.

### C. Evaluation of Pediatric Program

To obtain needed pediatric information on Gleevec, the FDA issued a formal Written Request to Novartis to submit the information on determining an MTD for all appropriate age groups, evaluation of pharmacokinetics, and determining Gleevec anti-leukemic activity in Philadelphia positive (Ph+) leukemia in pediatric patients who have recurrent or refractory acute

lymphoblastic or myeloblastic leukemia (ALL or CML) or chronic myelogenous leukemia (CML) with demonstrated resistance to interferon-alpha therapy.

This Supplement to the NDA 21-335 consists of the results from the two dose-escalation Phase 1 studies in children with Ph+ CML or Ph+ acute leukemias.

Phase 2 studies are being conducted in children with CML and variety of solid tumors (e.g., neuroblastoma, and osteosarcoma).

### D. Comments on Data Available or Needed in Other Populations

## X. Conclusions and Recommendations

### A. Conclusions

Support for approval of a Ph+ CML chronic phase leukemia indication in children comes mainly from clinical trials in adults with Ph+ CML. Gleevec received accelerated approval (AA) under subpart H for use in adults with Ph+ CML in accelerated phase, blast crisis and chronic phase after interferon alpha failure, based on hematologic response rate and cytogenetic response rate. AA is also imminent for adults with Ph+ newly diagnosed chronic phase CML, based on longer time to progression and longer time to accelerated phase or blast crisis.

Data from these two Phase 1 studies in children confirm that Gleevec can induce cytogenetic responses in children with Ph+ chronic phase CML with prior stem cell transplant or after failure of interferon alpha. There are sufficient data to support the Applicant's proposed dose of 260 mg/m2. Safety in children is similar to adults except that the incidence of edema and musculoskeketal pain is less in children.

### B. Recommendations

Gleevec is approvable under subpart H (AA) for treatment of children with Ph+ CML in chronic phase in recurrence after stem cell transplantation or after failure of interferon alpha therapy.

Deficiencies are:

(1) lack of a suitable formulation for children. The Applicant plans to submit a supplement for a scored 100 mg tablet that will remedy this deficiency.
(2) labeling revision is required (see the FDA review team's revised labeling).

The Applicant's Phase 4 commitment will be a satisfactory time-line for completion and submission of a study in children with Ph+ CML following the protocol for the Children's Oncology Group Phase 2 study previously submitted. This is conditional on changing the Gleevec dose in the protocol from 340 to 260 mg/m2.

# XI. Appendix

## A. Other Relevant Materials

**Detailed Review of Protocols**

**Study 0103**

"A Phase I, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for anti-leukemic effects of STI571 in pediatric patients with Ph+ Leukemia."

***Study Chairman – Children's Ocology Group:*** Martin Champagne, M.D.
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Montreal (Quebec) H3T 1C5, Canada

***Objectives:*** The primary objectives were to determine the maximum tolerated dose (MTD); to determine the dose-limiting toxicities (DLT) of STI571 in children with recurrent Philadelphia chromosome-positive (Ph+) leukemia; and to characterize the pharmacokinetic (PK) behavior of STI571 in this patient population. The secondary objective was to assess the anti-leukemic activity of STI571.

> ***Reviewer Comment:*** *The protocol stated that the "preliminary anti-leukemic effects will be assessed via three clinical response parameters: (1) peripheral white blood cell and leukemic blast counts (2) bone marrow leukemic blast infiltration (3) bone marrow cytogenetics." These responses were planned to be listed by dose cohort.*

Supplemental NDA 21-335/S-003 (sNDA), Study 0103 contains the primary (raw) data from the trial 0103, conducted in 23 centers (US 21 centers), and in 2 foreign countries (Canada 1 center and Australia 1 center). First patient accrued: February 26, 2000; last patient enrolled: September 4, 2001; data cutoff: March 19, 2002.

***Overall study design:***

The protocol is designed as a Phase I, multicenter, open-label dose-finding study of STI571 given orally daily for 28 days to pediatric patients with Ph+ Leukemia. Twenty eight daily doses of STI571 constitute one course. Two courses were given in the absence of progressive disease. Patients who did not show drug related toxicities will continue on therapy. STI571 pharmacokinec evaluations were performed on during Course 1 on Days 1 and 8. In this dose-escalating trial a standard design for determining the MTD has been used.

In the original protocol the oral dose of STI571 will commence at 260mg/m2/day (dose level 1). This starting dose was extrapolated from daily dose of 400mg that showed efficacy in adult patients with chronic phase CML.

> ***Reviewer Comment:*** *The clinical pharmacokinetics of Gleevec in children shows high interpatient variability. The exposure (AUC) from the 260 mg/m2 dose level was indistinguishable from the AUC of the 340 mg/m2 dose level. The was no apparent exposure-response relationship.*

***Eligibility criteria:***

- Male or female patients ≤21.99 years of age at study entry
- The patient must have a Ph+ leukemia and must have:
  - recurrent or refractory ALL or AML
  - CML with demonstrated resistance to interferon-alpha therapy
  - life expectancy >/= 8 weeks
- Prior therapy: patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering the study.
- Performance status: Karnofsky ≥50 for patients >10 years of age and Lansky ≥ 50 for children ≤10 years of age.
- Patients must not have received Busulfan or nitrosoureas within six weeks of Day 1, hydroxyurea, low dose cytosine arabinoside (< 30 mg/m2 every 12 to 24 hours administered daily) within 7 days of Day 1, moderate doses of cytosine arabinoside (100-200 mg/m2 for 5 to 7 days) within 14 days of Day 1, high-dose of cytosine arabinoside (1-3 g/m2 every 12 to 24 hours administered for 6 to 12 doses) within 28 days of Day 1.
- No other cytotoxic chemotherapies within 21 days of Day 1.
- Biologic (anti-neoplastic agent): At least 7 days since the completion of thrapy with a biological agent, including interferon-alpha.
- XRT: ≥ 2 weeks for local palliative XRT; ≥6 months must have elapsed if prior craniospinal XRT or if >/= 50% radiation of pelvis; ≥6 weeks must have elapsed if other substantial bone marrow radiation.

- Stem cell transplant: ≥3 months must have elapsed. Patients with controlled GVHD will be allowed on study.
- Concomitant medications: growth factor must not have been received within 1 week of entry onto this study.
- No use of anticonvulsants.
- All patients who participate in this study must have adequate organ function

Exclusion Criteria:

- Pregnancy or breast-feeding
- Patients who have an uncontrolled infection
- Patients receiving any other investigational agent
- All patients (or their legal guardians) must sign an informed consent that has been approved by the Institutional Human Review Committee.

***Patient Evaluation and Schedule of Tests***

All patients will undergo adequate pretreatment physical and laboratory evaluation, including physical examination, complete blood cell counts (CBC), serum chemistries, and bone marrow aspiration/biopsy with cytogenetics analysis.

During Course 1 and Course 2 of treatment, CBC, serum chemistries and pharmacokinetics studies will be repeated weekly. Bone marrow aspiration/biopsy will be repeated at the beginning of Course 2 and prior to subsequent courses if complete hematologic response (CHR) is suspected. with cytogenetics analysis.

Bone marrow cytogenetics analysis will be repeated prior to start of courses 3, 4, and 7. If the first hematologic response is provisionally diagnosed between weeks 13 & 25, a bone marrow aspirate and biopsy should be performed to verify remission.

The protocol stated that evaluation for safety will include all patients included in the study who have received at least one dose of study medication. Evaluation for efficacy will include all patients who receive at least one dose of study medication and for whom at least one efficacy evaluation after baseline is obtained.

***Dose-Limiting Toxicities:***

In this study dose limiting hematologic and non-hematologic toxicities are defined as following:

Non-hematologic dose-limiting toxicity is defined as any Grade III or Grade IV non-hematologic toxicity attributable to the investigational drug with the specific exclusion of:

- Grade III nausea and vomiting
- Grade III fever or infection

Since this protocol calls for the prolonged administration of STI571, any grade II toxicity causing a 7-day interruption of therapy prior to day 28 will also be considered dose limiting.

Hematologic dose limiting toxicity is defined as:
For patients with leukemia, DLT will be defined as a duration of bone marrow aplasia > 5 weeks from the first treatment day.

No intra-patient dosage escalation will be permitted on this study.

***Interruption or Discontinuation of Treatment:***

Grade II Non-Hematological Toxicity:
If a patient experiences Grade II toxicity that does not resolve despite symptomatic treatment, study drug should be withheld until the toxicity resolves to Grade I. If the toxicity resolves to Grade I within 7 days, study drug may be resumed at the same dose. If the toxicity recurs, study drug must be withheld until the toxicity resolves to Grade I. Upon recovery, study drug may be resumed at one dosage level lower than the initial dosage prescribed, or at a 30% dose reduction if the toxicity occurred at the first dosage level. If Grade II toxicity recurs, further dose reductions can be performed, using the above procedures.

Grade III/IV Non-Hematological Toxicity:
If a patient experiences Grade III/IV non-hematological toxicity the study drug must be withheld until the toxicity resolves. Upon recovery, study drug may be resumed at one dosage level lower than the initial dosage prescribed, or at a 30% dose reduction if the toxicity occurred at the first dosage level. If the Grade III/IV toxicity recurs, further dose reductions can be performed, using the above procedures.

Hepatic Toxicity:
Patients with SGOT/SGPT (ALT/AST) < 1 x ULN at baseline who experience > Grade III hepatic toxicity should be managed using the criteria detailed above. In patients enrolling with SGOT/SGPT > 1 x – < 3 x ULN at baseline and who experience < 5-fold increase in the levels of the most elevated transaminase, study drug will be withheld until the transaminase levels return to baseline values and then resumed at the same dose. If a similar degree of toxicity recurs, study drug must be held until the transaminase levels return to baseline values. Study drug may then be resumed at one dosage level lower than the initial dosage prescribed, or at a 30% dose reduction if the toxicity occurred at the first dosage level. If the toxicity recurs, further dose reductions can be performed, using the above procedures.

Grade III/IV Hematological Toxicity:
No dose modifications will be allowed during the first 28 days of therapy. If Grade IV neutropenia (ANC < 500/ul) is present on Day 28 or later, and does not resolve within 3 days of withholding STI571, a bone marrow aspirate and biopsy must be performed.

If marrow cellularity is <10%, study drug must be held until ANC > 1000/ul at which time treatment may be resumed at full dose. If Grade IV neutropenia persists, a bone marrow aspirate and biopsy will be performed weekly to assess the cellularity and percentage of blasts. If Grade IV neutropenia recurs after resuming trial treatment, study drug will be held until ANC > 1000/ul. Study drug will then be resumed at one dosage level lower than the initial dosage

prescribed, or at a 30% dose reduction if the toxicity occurred at the first dosage level. If the toxicity recurs, further dose reductions can be performed, using the above procedures.

If marrow cellularity is >10% and/or contains >30% blasts and/or is secondary to bone marrow fibrosis, treatment will be continued (or restarted if it has been withheld because of marrow hypocellularity and/or granulocytopenia). If Grade IV neutropenia persists for an additional week, a bone marrow aspirate and biopsy will be repeated and the above criteria applied. If Grade IV neutropenia persists for two weeks, study drug will be withheld (regardless of the bone marrow appearance) until ANC > 1000/ul at which time treatment will be resumed at full dose. If Grade IV neutropenia recurs, study drug will again be withheld until ANC > 1000/ul. Study drug will be resumed at one dosage level lower than the initial dosage prescribed, or at a 30% dose reduction if the toxicity occurred at the first dosage level. If the toxicity recurs, further dose reductions can be performed, using the above procedures.

***Criteria for removal from protocol therapy:***

a) persistent or progressive disease defined as:
- persistent leukemia after 2 courses (8 weeks of therapy)
- an increasing blast percentage in the bone marrow at day 29 (day 1 of course 2)
- recurrent leukemia after complete or partial response, or increase by > 30% in Ph+ bone marrow cells (Assessed either by standard cytogenetics or by FISH.)

b) dose-limiting toxicity
c) patient withdrawal from protocol

Patients who are off protocol therapy are to be followed until they meet the criteria for off study (see below). Follow-up data will be required.

***Off study criteria:***

a) Death
b) Irreversible dose-limiting toxicities
c) Lost to follow-up
d) Entry onto another POG/CCG therapeutic study.

***Safety Evaluation***

The protocol stated that "The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of the pre-determined ranges. Adverse events will be summarized by presenting, for each dosing cohort, the number and percentage of patients having any adverse event in each COSTART body system....."

NCI/NIH CTC grading system will be used to assess the hamatological and non-hematological toxicities.

***Statistical Considerations:***

Primary endpoints of this study were to determine the DLT and to determine the MTD of STI571 in children with recurrent Philadelphia chromosome-positive (Ph+) leukemia. Also, the pharmacokinetic (PK) behavior of STI571 was to be described in this patient population.

The starting dose for the first cohort of 3 patients was 260mg/m2/day (dose level 1). If none of these three patients experience DLT, then the dose is escalated to the next higher level (340mg/m2 – dose level 2) in the three subsequent patients.
If one of three patients experiences DLT at the current dose, then up to three more patients are accrued at the same level.

If none of these three additional patients experience DLT, then the dose is escalated in subsequent patients (440mg/m2 – dose level 3).

If one or more of these three additional patients experiences DLT, then patient entry at that dose level is stopped, the MTD has been exceeded and dose escalation will be stopped. Three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

If two or more patients experience DLT, then the MTD has been exceeded and dose escalation will be stopped. Three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

The MTD was defined as the dose level at which 0/6 or 1/6 patients experience DLT with at least 2/3 or 2/6 patients encountering DLT at the next higher dose. A maximum of 20 patients is anticipated. The final sample size will be determined by the results obtained during the course of the study.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose that is 30% lower then the starting dose.

> ***Reviewer Comments:*** *During the dose escalation the dose of Gleevec in mg/m$^2$ was rounded to the nearest 50 mg increment.*

***Protocol Amendments (Study 0103)***

The protocol was amended three times, on April 21, 2000, October 27, 2000 and March 14, 2001. The first amendment was a clarification to the eligibility criteria, included risk of hepatotoxicity, and additional instructions on administration of the drug to patients who are unable to swallow the capsules.

The second amendment add warning on potential risk of hemorrhages in patients who receive concomitant anti-coagulant therapy, and change in the dosing regimen (b.i.d. administration if the daily dose of STI571 was greater or equal to 800mg/day). Based on the regimen change, an appropriate changes were made to the pharmacokinetic sampling time points.

The third amendment included an additional number of patients (a total of 15), that the sponsor planned to enroll to the dose level 2 and 3 (340 and 440mg/m2, respectively). Escalation to the dose level 3 was permitted, if the previous dose of 340mg/m2 was well tolerated. The purpose of this change is to have a sufficient number of patients to minimize the "expected standard error of the mean of 2-fold and accurately describe the relationship between dose and the relevant parametrs."

> ***Reviewer Comments:*** *These protocol amendments were submitted before most of the patients had been accrued, therefore they are not considered to impact the integrity of the data or the validity of the trial results.*
>
> *Other changes in study conduct refer to the mid-2000, when the study became the responsibility of the Children's Oncology Group (COG) following the merger of the Pediatric Oncology Group (POG) with the Children's Cancer Group (CCG).*

**Study 03001**

"A phase 1, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles, and to evaluate for preliminary anti-leukemic effects of STI571A in patients with chronic myeloid leukemia resistant to IFN (Pediatric patients)"

> ***Study Chairmen:*** Brian J. Druker, MD
>
> ***Study period:*** First patients enrolled: 20-July-1999; Data cut-off date: 31-July-2001
>
> ***Objectives:*** To assess the safety and tolerability of STI571 when administered orally to Ph+ patients with CML resistant to IFN and to obtain pharmacokinetic profiles at different escalating doses. To obtain preliminary evidence of anti-leukemic activity as shown by a decrease in peripheral white blood cell and platelet counts and the percentage of Ph+ cells in the bone marrow.

Supplemental NDA 21-335/S-003 (sNDA), Study 03001 contains the primary (raw) data from the trial 03001, conducted in one center in the US (Oregon Health Sciences University).

Patient Exposure in Study 03001

Eight pediatric patients 5 to 17 years old were enrolled in one center, 3 with CML in chronic phase failing prior IFN, 4 with ALL, and 1 patient with lymphoid blast crisis.

> ***Reviewer Comments:*** *Study design, patient eligibility criteria, criteria for the dose escalation, dose reduction due to the non-hematological and hematological toxicities and statistical considerations were broadly similar for both studies (Study 0103 and Study 03001).*

*The notable difference in Gleevec dose administered in the Study 03001 compared to Study 0103 was that the actual dose was rounded to the nearest 25 mg in Study 03001 (dose was rounded to the nearest 50 mg in Study 0103).*

***Protocol Amendments (Study 03001)***

This study was amended 10 times. The rationale for amendments included an update for the serious adverse events reporting, increased safety evaluations in the presence of the hepatic toxicity; to prohibit use of the platelet reducing agent Agrylin; to specify when Allopurinol may be discontinued; to permit patients receiving corticosteroids and anticoagulants the opportunity to enter the study; to permit enrollment of patients who have received a prior bone marrow transplant.

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Supplemental NDA 21-335/S-003 for Gleevec
Phase IV Commitment

On December 20, 2002 the Food and Drug Administration issued Novartis a letter, which noted the completion of the review for the Supplemental NDA 21-335 / S-003 for Gleevec™, and it is approvable.

This Supplemental NDA contained efficacy and safety data from the two Phase 1 studies in a total of 39 pediatric patients with CML in chronic phase recurrent after stem cell transplant or resistant to interferon alpha therapy, or pediatric patients with Ph+ acute AML or ALL or CML in blast crisis refractory to or recurrent after multi-drug chemotherapy regimens. Based on these two studies Novartis provided labeling revisions for the use of Gleevec in children.

On May 9, 2003, Novartis submitted the following Phase IV commitment:

To submit a complete report on safety, efficacy and PK data from the ongoing NCI/COG Phase 2 Study No. AAML0123 using Gleevec at the 340mg/m2 dose to treat pediatric patients with: a) Ph+ newly diagnosed CML (34 patients); b) Ph+ CML in first chronic phase failing any prior treatment including interferon or intolerant of interferon (15 patients), and; c) Ph+ CML relapsing after transplantation or in second or subsequent chronic phase CML (15 patients). The data will be based on a data cut-off of 2 years following FPFV. The study report is estimated to be available in 2Q05."

The proposed by the sponsor Phase 4 commitments are satisfactory for an approval of Gleevec for treatment of pediatric patients with CML in chronic phase recurrent after stem cell transplant or resistant to interferon alpha therapy,

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